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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/068,916	RITTER ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 7/11/03 and a request for continued examination filed 1/12/04. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/12/04 has been entered. Claims 49-58 have been added. Claims 21, 25, 30, 35, and 40-43 have been amended. Claims 18-59 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-27, 35-41, 46 and 49-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21-24 and 49-58 recite the limitation "the graft-recipient T cell" in claim 21. There is insufficient antecedent basis for this limitation in the claim.

Claims 21-27 and 49-58 are vague and indefinite in that the metes and bounds of, "a mixed lymphocyte culture" are unclear. The claims recite (in line 9 for claim 21 and line 7 for claim 25) that the mixed lymphocyte culture comprises the isolated lymphocyte that is an irradiated T cell, an irradiated cell that expresses a dominant MHC molecule, or a recipient T

cell. In a second reference, the claims recite (in line 12 for claim 21 and line 11 for claim 25) that the mixed lymphocyte culture comprises a donor T cell or cell, which expresses a dominant MHC molecule with a recipient T cell. While these mixed lymphocyte cultures appear to be the same culture, the fact that they are referred to with distinct terminology in each definition is confusing. It would be remedial to delete the second definition of a mixed lymphocyte culture.

Claims 35-41 recite the limitation "the therapeutic gene" in claim 30. There is insufficient antecedent basis for this limitation in the claim.

Claim 39 recites the limitation "the T cell" in claim 30. There are two T cells recited in claim 31, the gene modified T-cell and the graft-recipient–specific T-cell. Therefore, it is unclear which of these is referred to in claim 39.

Claims 39-41 are vague and indefinite in that the metes and bounds of, "a mixed lymphocyte culture" are unclear. It appears that the mixed lymphocyte culture comprises the graft recipient-specific T cell but there is no actual connection between the two in the claim language. The connection between the graft recipient-specific T cell and the mixed lymphocyte culture should be made clear.

Claims 46, 51 and 55 are vague and indefinite in reciting that a T cell of the graft recipient is stimulated. The *in vitro* modified T cell of claim 18, which is used to treat a patient for allogeneic graft rejection is previously stimulated in vitro with a cell of a graft donor. Therefore, it is unclear if the step of stimulating in claim 46 is performed *in vitro* simultaneously or after the first stimulation or if the step of stimulation in claim 46 is performed once again prior to treatment. Furthermore, it is unclear with what the T cell is stimulated.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention is drawn to a method of *in vitro* generation of modified T cells comprised of stimulation of a recipient T-cell by contact with cells of a graft donor. This invention requires a combination of molecular cloning, viral, cell culture and clinical techniques.

2) **Scope of the invention**. This invention further recites genetic modification of the stimulated recipient T cells by *ex vivo* transfer of therapeutic genes into the T-cells utilizing retroviral vectors or liposomes or a gene gun and methods of treatment for allogeneic graft failure using the modified T cells. The only disclosed use of the modified T cells is for the prevention of graft rejection. Use of retrovirus for transfer of the therapeutic gene into the graft

recipient T cell exacerbates a complicated method. Additionally, use of the *in vitro* modified T cell in gene therapy protocols further exacerbates a complicated method.

3) **Number of working examples and guidance**. The specification provides by way of working examples, generation of modified T cells expressing IL-4, IL-10, IL-12p40. The coding sequences are transferred into T cells using amphotrophic retroviral cells lines.

An *in vitro* model system was developed to demonstrate effectiveness of the inhibition of proliferation of naïve T cells. In this model, stained recipient cells and irradiated stimulator cells (graft-specific cells) were incubated with transgenic vIL-10 lymphocytes and proliferation and interferon-γ production was inhibited (page22,line 1-16) . Additional guidance included methods for transferring therapeutic genes into T cells using non-viral methods and non-retroviral vector systems such as lentivirus, AAV and CMV based viral delivery systems (page 22, line 18 through page 23, line 16).

4) **State of Art**. The state of transplant medicine art historically utilized compounds such as cyclosporin A, glucocorticoids and OKT3 to ensure transplantation by suppressing an immune response. However, these treatments require long-term exposure and often are associated with immunosuppression complications. Another means of suppressing immune responses though T-cell depletion was found to be limited in success in ensuring graft acceptance. More recently, approaches to ensuring graft acceptance have focused on altering the graft versus host disease response. Targets have primarily been the altering or masking of the immune response of the donor cells. These are currently under much research. Level of skill in the art. The level of skill in the art covering this invention was not high at the time of invention. The development of

was rapidly advancing in the field. But the field of gene therapy was just beginning to emerge including preclinical trials and animal models.

5) **Unpredictability of the art.** The art of *ex vivo* gene therapy in which cells are modified *in vitro* and then transduced back into the patient are highly unpredictable. As a first problem is the method of transducing cells with the transgene of interest. While several methods for introducing DNA into the cells are contemplated such as retroviruses, other viral vectors, liposomes and gene gun. Typically, methods of transducing DNA into cells lacks efficiency and stable gene expression is lacking. Use of retrovirus has been developed to overcome these obstacles. Retrovirus mediated gene transfer is one of the preferred method of transfer in the instant application. As noted by Marshall, (Marshall et al., Science January 17, 2003) one of the main issues in using retroviral vectors for gene therapy is determining how to use the vector in vivo without causing leukemia or other cancers in the patients being treated. This is not merely a safety issue for FDA concern but is a fundamental issue underlying how the skilled artisan can make and **use** the claimed invention for the recited treatments. As further reported in Romano (Drug News and Perspective, 2003), ex vivo retrovirally mediate gene transfer caused leukemia and with AAV caused tumors in mice (page 2, paragraph 2-3).

Often when cells are transduced back into the patient, sustained reliable expression is not maintained. Additionally, the efficiency of transplantation of the infected cells is another challenge to the success of this therapy. Limitations of T-cell delivery of therapeutic genes for human use include, the lack of efficiency of gene transfer to stem and primary cells, sustained tolerance to the gene modified T cells, prolonged survival of the genetically modified cells. Some regimens have observed a lack of sustained persistence of these cells (Greenberg et al,

2001). Much promise has been proposed for IL-10 claimed in invention also. However, IL-10 has been reported to under some circumstances act as an immune stimulant for T-cell mediated responses *in vivo* (Zeller, page 3684, column 2, line 1-3) depending on the dose (page 3890, column 1, line 1-5). Gene therapy protocols have demonstrated that cytokine production is not associated with prolonged graft acceptance (page 608, column 1, paragraph 3) while IL-10 expression is associated with alloreactive responses (page 608, column 2, paragraph 2) (Bagley and Iacomini, Gene Therapy, 2003).

The unpredictability of using the claimed invention for use in humans is mitigated due to the lack of methods or processes disclosed in the specification. Many parameters must be addressed for *in vivo* use and yet there are no methods or means disclosed such as delivery methods for the introduction of the modified cells into humans, means of preparing the T-cells for *in vivo* applications, which genes and the safety of their use, biosafety issues of transfection protocols and efficiency of transgene expression. Many *in vitro* and animal models that are provided as evidence of success of treatment have not translated into successful treatment in humans. The *in vitro* assays with modified T cells generated according to the invention provide evidence that use of transgenic T cells expressing vIL-10 *in vitro* has promise. However, *in vitro* results have not always correlated well with *in vivo* clinical trial results in patients. In the case of transplant acceptance, "making it difficult to find an *in vitro* correlate of *in vivo* tolerance" (Waldmann, 1998). In reality, success of gene therapy of any condition in humans is extremely limited.

6) **Summary**. The invention recites a complex series of methods for the generation of in vitro modified T cells and uses of the T cells for graft acceptance. The unpredictability of using

the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of established clinical protocols and the inability to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Arguments

Applicant traverses the rejections under 35 U.S.C. 112, first paragraph on pages 2-3 of the amendment filed 1/12/04 by referencing the Declaration filed 1/12/04 by Dr. Kupiec-Weglinski as teachings that the invention is enabled. Applicants further argue that any reference to general statements in various publications is not applicable here because the references have not reviewed the discovery of present inventors nor assessed the pending claims. Rather, from the two Declarations from two experts it can be concluded that the presently claimed invention is, in fact, enabled.

The Declaration of Dr. Kupiec-Weglinski states that 1) the idea of using *ex-vivo* generated alloantigen-specific T cells to carry immunomodulatory molecules is a desirable approach that **may** well fulfill the goal of transplantation. 2) retrovirus mediated gene transfer is

not the only method provided in the specification to transduce T cells 3) Hori et al have shown promising data in the generation of regulatory cells *ex vivo* with regulatory *in vivo* properties. 4) Dr. Kupiec-Weglinski is convinced that *in vitro* IL-10 modified T cells will exert potent regulatory function in vivo.

The Declaration and exhibits under 37 CFR 1.132 filed 12/19/02 are insufficient to overcome the rejection of claims 18-59 based upon 35 U.S.C. 112, first paragraph, as set forth in the Office action because of the following reasons:

The instant invention does not teach methods for clinical or pre-clinical use of the proposed invention such that the instant invention can be used. Essential factors not taught include treatment intensity, accompanying immuno-suppression drugs and schedule of treatment as well as amount of retrovirus to be used. Details for *in vivo* gene therapy following retroviral transfer into the T cells are not adequately taught in the specification. Specifically, the instant specification teaches the generation of in vitro modified graft recipient T cells from a mixed lymphocyte culture (origin unstated), bioassays for expression of therapeutic genes and *in vitro* analysis of their immuno-regulatory potential. These teachings in no way provide the skilled artisan with the ability to use these cells to treat a patient for allogeneic graft rejection in a predictable fashion. No *in vivo* protocol steps or teachings are provided for in the specification.

The teachings of the prior art do not teach how to **use** the instantly claimed invention. Any successes recited in Hori et al cannot be extrapolated back to the instant invention because the instant specification lacks support for the teachings of said references. In Hori et al, CD25-4+ T cells are transduced with retrovirus expressing Foxp3/MIGR1 and stimulated with CD3mAb or OVA peptide. The cells exhibited suppressed proliferation with an associated

inhibition of IL2 expression. Furthermore, inflammation and autoimmune disease was "prevented" in SCID mice. Neither these teachings nor the specification provide the specific dosages to be administered to patients, the schedule of treatments, and the specific modes of administration etc for the *in vitro* modified cells of the invention. Therefore, the teaching of the specification and prior art do not teach one how to use the *in vitro* modified T cells for therapeutic purposes.

Finally, the publications that have been provided have been used to provide evidence that at the time of filing, undue experimentation would have been required to use the instant invention. There should be no expectation that publications that do not directly review the discovery of present inventors nor assess the pending claims are not applicable. In fact, the adequacy of the disclosure can only be evaluated in reference to current knowledge at the time of filing and the provided references were provided to elucidate the current environment of gene mediated transfer for transplantations.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

February 20, 2004

GERRY LEFFERS
PRIMARY EXAMINER